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# Intravenous bumetanide attenuates the rise in plasma vasopressin concentrations during major surgical operations

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During a study in seven patients on the endocrine response to major surgical procedures under general anaesthesia an incidental finding was that the administration of intravenous bumetanide prior to surgical stimulation led to reduced concentrations of plasma vasopressin (AVP) when compared with a control group of patients.

**Keywords** bumetanide vasopressin surgical operations

## Introduction

The metabolic effects of hormonal release during surgical procedures are complex and have recently been reviewed by Bevan (1980), Kaufman (1982) and Traynor & Hall (1983). Philbin *et al.* (1979) found that large doses of intravenous morphine (2 mg $kg^{-1}$) were able to suppress the ADH secretion during cardiac surgery until the onset of cardiopulmonary bypass whereas Bonnet *et al.* (1982) showed that extradural anaesthesia suppressed ADH secretion during surgery for total hip replacement. In a study of the endocrine response to major surgical procedures it was noted that the urinary output was often markedly decreased necessitating the use of a diuretic despite adequate fluid intake. Prior to surgical stimulation, which causes an increase in AVP release (Melville *et al.*, 1985), a diuretic, bumetanide, was administered in an attempt to maintain an adequate urinary output.

## Methods

Seventeen patients undergoing elective major abdominal surgery including anterior resection and abdomino-perineal resection of rectum were randomly allocated to two groups, A (Control) and B (Bumetanide). The patients in group B were given a bolus injection of bumetanide (0.0075 mg $kg^{-1}$) 5 min prior to initial surgical incision. There was no significant difference for age (Group A—49 years ±5.2: Group B—51 years ±8.5) or weight (Group A—59.5 kg ±4.0: Group B—65.1 kg ±4.4). They were in ASA groups 1 or 2 and none had received corticosteroid therapy in the previous year (ASA = American Society of Anesthesiologists' classification of physical status).

All the patients were premedicated with papaveretum 10 mg and hyoscine 0.2 mg. Induction was with etomidate (0.2 mg $kg^{-1}$) and suxamethonium (0.8 mg $kg^{-1}$) for intubation and thereafter anaesthesia was maintained with diamorphine 0.1 mg $kg^{-1}$ in a bolus dose and incremental doses of atracurium for muscle relaxation (initial dose 0.3 mg $kg^{-1}$ and subsequent doses of 0.15 mg $kg^{-1}$ at half hourly intervals). The patients were ventilated with nitrous oxide and oxygen and the ventilation (intermittent positive pressure ventilation—IPPV) adjusted to maintain an end-tidal $CO_2$ concentration of 4.0–4.5% (Datascope Capnograph). The last dose of atracurium was administered at least 0.5 h before the end of surgery so that spontaneous respiration resumed without reversal of the muscle relaxant. The doses of drugs used were comparable in both groups.

The heart rate was monitored by Cardioscope and the mean arterial pressure recorded automatically (Dinamap 845 with printer). Blood

samples were taken preoperatively and pre-induction from a large peripheral vein and thereafter samples were drawn through a central line which had been inserted into the right internal jugular vein following induction of anaesthesia. Samples were taken at hourly intervals during surgery and at hourly intervals for the first 5 h following the end of the operation. A final sample was taken 24 h post-operatively. Blood loss, which was assessed by swab weighing, and was comparable in both groups, was only replaced via a peripheral venous line. The patients' normal daily requirement of fluid and electrolytes was administered by constant infusion of Ringer lactate solution, 8 ml $kg^{-1}$ $h^{-1}$. Thus one line was kept separate for blood replacement and the other for sampling and administering electrolytes, thereby avoiding contamination of samples. The central venous pressure was maintained between 3 and 6 cm of water.

After collection each blood sample was immediately centrifuged, the plasma being stored at −20° C until analysed for arginine vasopressin (AVP) by radioimmunoassay technique (Aziz *et al.*, 1981). Plasma osmolality was measured by depression of freezing point using a Cardiac Recorders' osmometer (CR30).

An indwelling urinary catheter was connected to a urinometer collecting device. The initial urine sample was measured 0.5 h after induction and thereafter measurements of urine volume were made at hourly intervals.

## Results

Results displayed are based on the means of the seven patients and 10 controls (± s.e. mean).

Hypotension occurred following the introduction of IPPV, but there was no significant difference in the mean arterial pressure, heart rate and plasma osmolality between groups A and B.

### *AVP*

Pre-induction and post-induction plasma concentrations of AVP were similar in both groups but measurements made 0.5 h after induction showed that there was a significant difference between the groups, 25 fmol $ml^{-1}$ in the control group whereas in the bumetanide group it had reached only 10 fmol $ml^{-1}$ (*t*-test: $P < 0.05$). The difference remained significant during whole surgical procedure and for 5 h in the postoperative period (*t*-test: $P < 0.05$ at 2.5 h, 3.5 h from incision and at 1 h, 2 h, 3 h, 4 h and 5 h post-operatively). The maximum plasma level in the control group was 35 fmol $ml^{-1}$. The last measurement made 24 h postoperatively showed that the levels were similar in both groups (Figure 1).

### *Urinary output*

The first measurement of urinary output 30 min following surgical stimulation showed there was a significant increase in the bumetanide group (B) (*t*-test: $P < 0.05$). The urinary output in group B reached a maximum of 4 ml $kg^{-1}$ $h^{-1}$ compared with 1 ml $kg^{-1}$ $h^{-1}$ in the control group after a period of 2 h although 1 h post-operatively the urinary output was similar in both groups (Figure 2).

## Discussion

The purpose of this study was to ascertain whether the administration of a diuretic prior to surgical stimulation, which releases AVP, could still lead to a diuresis. The surprising finding was that the administration of a small dose of the loop diuretic bumetanide in addition to increasing urinary output also attenuated the rise in plasma ADH levels in response to surgical stimulation. There was little alteration in plasma osmolality, an increase of which can lead to AVP secretion.

The groups of patients were evenly matched for age, weight and extent of the major surgical procedure, anaesthetic technique including drug dosage and blood replacement. There was little difference between the groups in the mean arterial pressure which can affect AVP secretion. Intermittent positive pressure ventilation (IPPV) especially with positive end-expiratory pressure (PEEP) can impair renal function and lead to an increase in AVP release, but this would apply equally to both groups (Priebe *et al.*, 1981; Annat *et al.*, 1983). Alterations in intra-thoracic volume affect AVP secretion (Epstein *et al.*, 1977) but blood loss and fluid replacement were again comparable in both groups.

A study in conscious volunteers showed that loop diuretics had no effect on resting plasma AVP levels although an increased response had been expected from the resulting reduction in blood volume (Bayliss & de Beer, 1981). During general anaesthesia surgical stimulation results in a marked increase of AVP levels far in excess of that required for maximum anti-diuresis (Fieldman *et al.*, 1985). The main stimulus for AVP release appears to be peritoneal stimulation (Melville *et al.*, 1985).

Bumetanide was used in preference to other loop diuretics because of its potency and bio-

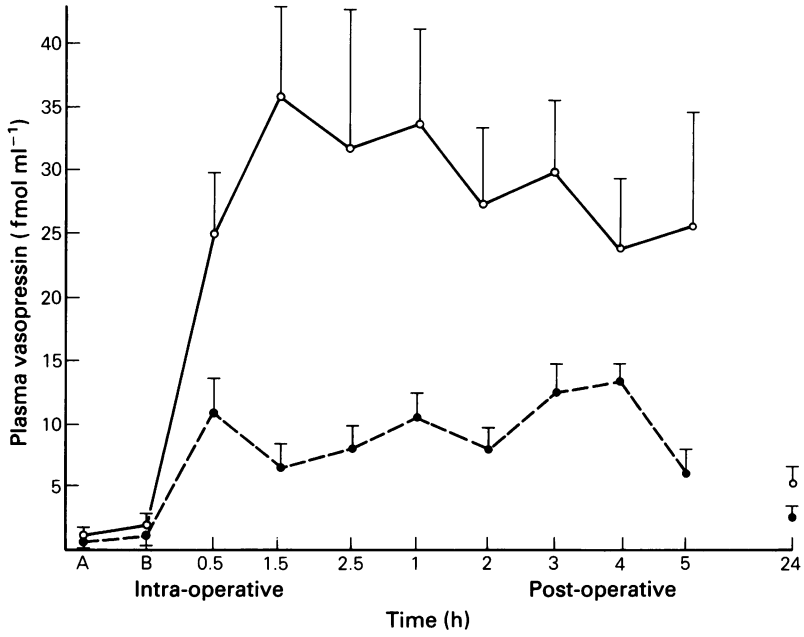


**Figure 1** Plasma vasopressin during the study period (mean ± s.e. mean) in the control group (○) and bumetanide group (●); A—preinduction, B—postinduction.

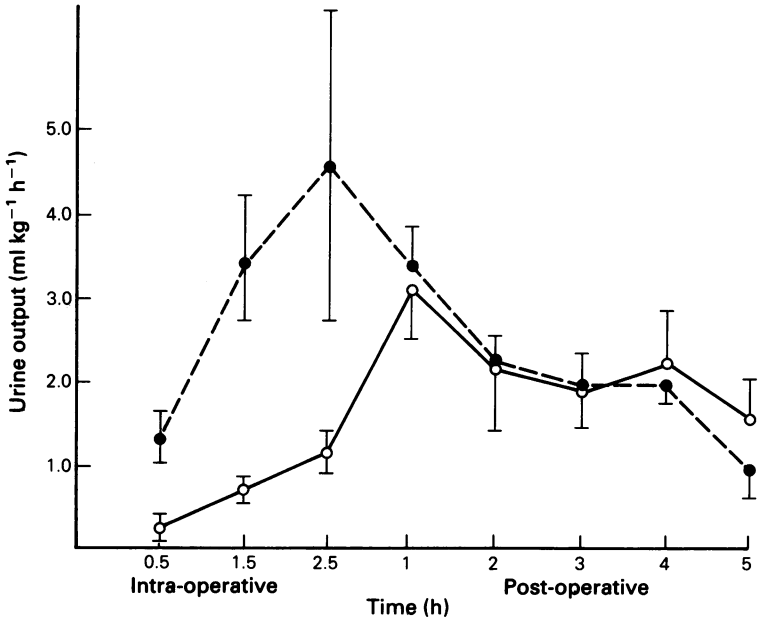


**Figure 2** Urine output during the study period (mean ± s.e. mean) in the control group (○) and the bumetanide group (●).

availability (Brater, 1986) and because it appears to lack the acute vascular effects of frusemide which releases renin from the kidney (Johnston *et al.*, 1986). The ampoule of bumetanide contains 0.5 mg $ml^{-1}$ of bumetanide, 45 mg $ml^{-1}$ zylotol, (a preservative) polyhydric alcohol related to zylose, and also a phosphate buffer and it is improbable that the amount of preservative would alter AVP levels. Bumetanide given before the surgical incision attenuated the expected rise in plasma levels of AVP during the course of surgery and for at least 5 h in the postoperative period, outlasting the duration of its effect on the urinary output.

The explanation of the effect of bumetanide remains obscure. Bumetanide is unlikely to influence the destruction of AVP which has a short half-life of approximately 18 min and which is usually inactivated in the liver and kidneys. It is also doubtful that the fall in plasma level of AVP was due to increased excretion of the hormone: urinary levels are unrelated to plasma levels (Fieldman *et al.*, 1985).

It thus appears that bumetanide may have a central action preventing the release of AVP in response to surgical stimulation during general anaesthesia. There is a possibility that the results may have been influenced by the use of etomidate, an induction agent which suppresses the cortisol response to surgical stimulation and which leads to increased plasma ACTH levels (Fellows *et al.*, 1985). However, these changes occurred much later in the operation than those seen in AVP.

The amount of AVP secreted during major surgical procedures is in excess of that necessary for maximum anti-diuresis (Fieldman *et al.*, 1985). The administration of bumetanide given prior to surgical stimulation may maintain urine output. It remains to be determined whether any other diuretics share the property of preventing the vasopressin response during surgery.

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## References

Annat, G., Viale, J. P., Bui Xuan, B., Hadj Aissa, O., Benzoni, D., Vincent, M., Gharib, C. & Motin, J. (1983). Effect of PEEP ventilation on renal function, plasma renin, aldosterone, neurophysins and urinary ADH, and prostaglandins. *Anesthesiology*, **58**, 136–141.

Aziz, L. A., Forsling, M. L. & Woolf, C. J. (1981). The effect of intracerebro-ventricular injections of morphine on vasopressin release in the rat. *J. Physiol.*, **311**, 401–410.

Baylis, P. H. & De Beer, F. C. (1981). Human plasma vasopressin response to potent loop-diuretic drugs. *Eur. J. clin. Pharmac.*, **20**, 343–346.

Bevan, D. R. (1980). Metabolic response to anaesthesia, surgery and trauma. In *General Anaesthesia* 4th edn, eds Gray, T. C., Nunn, J. E. & Utting, J. E., pp. 1017–1036. London: Butterworths.

Bonnet, F., Harari, A., Thibonnier, M. & Viars, P. (1985). Suppression of antidiuretic hormone hypersecretion during surgery by extradural anaesthesia. *Br. J. Anaesth.*, **54**, 29–36.

Brater, D. C. (1986). Disposition and response to bumetanide and furosemide. *Am. J. Cardiol.*, **57**, 20A–25A.

Epstein, M., Pins, D. S., Sancho, J. & Haber, E. (1975). Suppression of plasma renin and plasma aldosterone during water immersion in normal man. *J. clin. Endocrinol. Metab.*, **41**, 618–625.

Fellows, I. W., Yeoman, P. M., Selby, C. & Byre, A. J. (1985). The effect of anaesthetic induction with etomidate on the endocrine response to surgical trauma. *Eur. J. Anaesth.*, **2**, 285–290.

Fieldman, N. R., Forsling, M. L. & Le Quesne, L. P. (1985). The effect of vasopressin on solute and water excretion during and after surgical operations. *Ann. Surg.*, **201**, 383–390.

Johnston, G. D., Nicholls, D. P., Kondowe, G. B. & Finch, M. B. (1986). Comparison of the acute vascular effects of frusemide and bumetanide. *Br. J. clin. Pharmac.*, **21**, 359–364.

Kaufman, L. (1982). The endocrine response to surgery and anaesthesia. In *Scientific Foundations of Anaesthesia* 3rd edn, eds Scurr, C. A. & Feldman, S., pp. 290–307. London: W. Heinemann.

Melville, R. J., Forsling, M. L., Frizas, H. I. & Le Quesne, L. P. (1985). Stimulus for vasopressin release during elective intra-abdominal operations. *Br. J. Surg.*, **72**, 979–982.

Philbin, D. M., Coggins, C. H. & Emerson, C. W. (1979). Plasma vasopressin levels and urinary sodium excretion during cardiopulmonary bypass. Comparison of halothane and morphine anaesthesia. *J. thorac. cardiovasc. Surg.*, **77**, 582–585.

Priebe, H. J., Heimann, J. C. & Hedley-White, J. (1981). Mechanisms of renal dysfunction during positive end-expiratory pressure ventilation. *J. appl. Physiol.: Respirat. Environ. Exercise Physiol.*, **50**, 643–649.

Traynor, C. & Hall, G. M. (1981). Endocrine and metabolic changes during surgery: anaesthetic implications. *Br. J. Anaesth.*, **53**, 153–160.

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